Remarks

Claims 1-3, 5-8, 10, 12-15 and 45 remain pending.

Priority Date:

It is respectfully submitted that the priority date for the instantly claimed application serial number 09/782841 should be application serial number 09/139,861. Reference may be made to page 3, lines 19-28 and page 4, lines 20-26. One of ordinary skill in the art would appreciate the disclosure of the limitations of the presently claimed invention.

Claim Rejection: 35 U.S.C. §112, second paragraph

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected as being indefinite for use of the language "proximate said primary tumor site." Claims 1 and 45 have been amended to use the language "proximate to said primary tumor site."

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected as being indefinite because it is not clear "what the claimed molecular and cellular factors and cells are." It is respectfully submitted that those of ordinary skill in the arts would appreciate and understand what the term "molecular and cellular factors and cells" are. Examples of such factors and cells are provided within the prior art of record. Reconsideration of this rejection is requested.

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected as being indefinite because it is not clear what "other" immununologic anti-tumor cell specific products and cells are. The word "other" in claims 1 and 45 has been removed.

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected as being indefinite because it is not clear in claims 1 and 45 what "photodynamic light therapy released tumor cell specific antigens" are. Claims 1 and 45 have been amended to more clearly indicated that the tumor cell specific antigens are released as a result of the photodynamic light therapy.

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected under 35 U.S.C. §112, second paragraph, pertaining to the use of the term "approximately." Amendments to claims 1 and 45 have been made to more clearly define the Applicant's invention.

Claims 1-3, 5, 7-8, 10, 12-15 and 45 were rejected under 35 U.S.C. §112, second paragraph, because in claims 1 and 45 it is not clear whether the light or the photosensitizing agent or both are administered proximate to the primary tissue site. Appropriate correction has been made to claims 1 and 45.

Claim 7 and 8 were rejected as being indefinite for the use of the language "DETOX" which is a trademark. Correction has been made to claims 7 and 8.

Claim Rejection: Rejection under 35 U.S.C. §103

Claims 1-3, 5, 7-8, 10 12-15 and 45 were rejected under 35 U.S.C. §103 as being unpatentable over Bellnier, DA, 1991, J Phochem. Photobiol, B:Biol, 8:203-210, in view of US 4,963,354, Krosl et al, 1996, Cancer Res, 56(14): 3281-6, Canti G et al, 1994 Anti-Cancer Drugs, 5: 443-447, Sakurai et al, Malik, A et al, Matsumoto, Y et al, and Kim et al. Reconsideration of the rejection of claims 1-3, 5, 7-8, 10 12-15 and 45 is solicited.

The Applicant's claims are directed to systemic eradication of metastatic tumors specifically targeted by a systemic immunological interaction between the heightened level of macrophage cells (resulting from the adjuvant administration) and the PDT-released tumor specific antigens. Cancer cells of the metastatic tumor are specifically targeted by the system-wide tumor-specific antibodies, said antibodies being specifically targeted to the metastatic tumor as a result of the immunologic interaction between the increased level of tumor cell specific antibodies and the PDT-released tumor specific antigens.

Bellnier et al. teaches that photodynamic therapy of mice is potentiated by intravenous administration of tumor necrosis factor-alpha (TNF). Unlike the invention as presently claimed, the administration of TNF does not result in a systemic condition of heightened nonspecific

enhanced immune system of the body, including an increased level of macrophage cells which interact with tumor cell specific antigens released during a photodynamic light therapy. TNF promotes a different non-specific modality to direct tumor cell eradication as compared to the immunologic tumor cell specific eradication of the present invention, as TNF "induces hemorrhagic necrosis in solid tumors and has cytostatic or cytotoxic effects on mouse and humor tumor cells in vitro." Pages 203 – 204. Bellnier teaches that a combination therapy is desirable to improve therapeutic effect (page 204). Bellnier teaches an additive effect of a combination therapy, as "[t]he data also show that, although rHuTNF-α potentiates the PDT of tumor tissue, it has little effect on normal foot tissue, i.e. the combination therapy retains the therapeutic selectivity of the individual treatment modalities." Page 209, lines 3 – 6. Bellnier et al. teaches, as does Krosl et al., that direct PDT killing of tumor cells may be improved by combining an adjuvant with the photodynamic therapy. Importantly, Bellnier et al. does not teach or suggest a tumor cell specific immunologic response resulting in metastatic tumor eradication initiated via an administration of an immunologic adjuvant and photodynamic therapy at a primary tumor.

Krosl G. et al discloses a photodynamic eradication of local tumor cells utilizing a photosensitizer agent and a light source. The eradication of the local tumor cells in Krosl is not via a systemic immune response, as claimed by the Applicant's present invention. Rather, Krosl G. et al discloses tumor eradication via well known phototoxic mechanisms, i.e., peroxidation of membranous lipids and proteins resulting in cell necrosis. Krosl G. et al. discloses an in vivo local administration of murine granulocyte-macrophage colony-stimulating factor (GM-CSF). Krosl G. et al discloses that "[t]he tumor-localized GM-CSF immunotherapy alone had no obvious effect on the growth of parental SCCVII tumors." Abstract. Krosl G. et al. discloses that "GM-CSF treatment did increase the cytotoxic activity of tumor-associated macrophages against SCCVII tumor cells." Abstract.

Krosl G. et al discloses the use of an immunologic adjuvant (GM-CSF) to increase the local uptake of the photosensitizer agent (via increased levels of macrophages) into the tumor. Krosl G. et al discloses improved tumor photoeradication by increasing the local uptake of the

photosensitizer agent (via the increased macrophage level) by the tumor. Mechanistically, the immunologic adjuvant of Krosl is administered to increase the local macrophage level to effect an increased local uptake of the photosensitizer agent by the tumor (as macrophages are known to preferentially accumulate photosensitizers), and not as presented in the subject matter of the Applicant's present invention, to facilitate a systemic immunological response to target to metastatic tumor cells. *See, Korbelik, M, and Krosl, G. Photofrin accumulation in malignant and host cell populations of various tumors; and Krosl, G. and Korbelik, M., Potentiation of photodynamic therapy by immunotherapy: the effect of schizophyllan (SPG),* copies attached.

Importantly, Krosl G. et al does not teach that the adjuvant is administered to promote a systemic immunologic response for treating metastatic tumors as claimed by the present invention. Krosl et al. does not teach or suggest that the adjuvant is administered to create a systemic immunization condition including an increased level of macrophage cells necessary for an immune response. Indeed, Krosl G. et al specifically teaches away from a systemic immunological approach to metastatic tumor cell eradication, as Krosl G. et al states:

> Since *systemic treatment* with high does of GM-CSF may lead to profound perturbations in hemopoiesis and induce serious side effects (14) and i.v. injected GM-CSF has a relatively short half-life (2h), it would be preferable if a means could be developed to achieve a sustained local release of this cytokine at the tumor site. Krosl, Page 3281, Column 2, lines 43-49 (emphasis added).

Krosl et al. teaches away from the present invention by expressly warning that an element of applicant's invention, namely the administration of the immunologic adjuvant to create a systemic immunologic response, "should not, or cannot be used." *See, Dow Chem. Co. v. American Cyanamid Co., 816 F.2d 617, 2 USPQ2d 1130 (1131 (Fed. Cir. 1994).*

Canti et al. discloses the effects of PDT with photoactivated ALS_2Pc on antitumor immunity (page 446). Canti et al. discloses that animals surviving 100 days after PDT with photoactivated ALS_2Pc which were rechallenged with the parental tumor via intradermally injected tumor cells survived indefinitely, suggesting that PDT was able to induce a strong antitumor immunity (page 444, 446). Canti et al. purportedly teaches passive specific tumor cell

immunity against subsequently reintroduced identical tumor cells. Importantly, Canti et al. does not disclose or suggest the formation of a metastatic tumor specific immune response targeted against metastatic tumor cells existing within the living body at the time of photodynamic therapy as presently claimed.

Applicant submits that it is known to those skilled in the art that photodynamic therapy may induce an immunologic effect. Canti et al. discloses that some photodynamic therapies induce immunosuppression (page 443, second column) while other photodynamic therapies may induce immunopotentiation. However, Canti et al. does not "teach" or disclose a method for immunologic antitumor immunity against metastatic cancer cells of the living body as presently claimed, but merely identifies a particular recognized need that "it would be advantageous if the metastasized or undestroyed cancer cells could be eliminated immunologically rather than through chemotherapy" (page 446).

It is known that photodynamic therapies may induce an immunologic effect, as taught by Canti et al., wherein some photodynamic therapies induce immunosuppresion (*See*, Lunch et al. and Musser et al.), and wherein others induce immunopotentiation. It is also known that combination therapies of PDT and an immunologic adjuvant have an additive or complementary effect toward eradication of cells within the PDT treatment field, as taught by Krosl et al. and Bellnier et al, whereby two different modalities are combined to eradicate cells. Additionally, it is known that adjuvants alone can be used for treating metastatic tumors, as taught by Sakurai et al, Lofthouse et al, Malik et al, and Matsumoto et al, although involving a different mechanism of tumor cell eradication via a non-specific anti-tumor immunologic response. However no teaching or suggestion is found in the prior art to support a rejection of the present claims by the combination of Krosl, Bellnier, Canti, Sakurai, Lighthouse, Malik, and Matsumoto as proposed in the previous office action. There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the art would make the combination to achieve the subject matter of the present claims. *See*, Symbol Technologies, Inc. v. Opticon Inc., 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991). Since no such reason, suggestion or motivation exists, the pending claims are not obvious in view of the known prior art.

Even assuming that the combination of Krosl, Bellnier, Canti, Sakurai, Lighthouse, Malik, US 4,963,354, Kim and Matsumoto as proposed in the previous office action was correct, the combination of references would fail to disclose or teach the invention as presently claimed. The step of promoting and enhancing a systemic immunologic response of said body as a result of an interaction between the increased level of tumor cell specific antigens released during the photodynamic light therapy, said systemic immunologic response yielding increased levels of tumor cell specific antibodies for eradicating cells of the remotely disposed metastatic tumor and yielding a reduction in a metastatic tumor size, is not disclosed or taught by the combination of references. As a result, reconsideration of the rejection of claims 1-3, 5, 7-8, 10 12-15 and 45 is solicited.

Request for Reconsideration and Allowance

Based upon the above Amendments and Remarks, claims 1-3, 5, 7-8, 10 12-15 and 45 are believed to be in proper form for allowance, and patentable over the prior art made of record. Applicant respectfully requests reconsideration of those claims and a prompt Notice of Allowance thereon.

Please direct any questions regarding this application to John Klos at (612) 321-2806.

Respectfully submitted,
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